uble, and the suspension treated with anhydrous hydrogen chloride. The precipitate was extracted with petroleum ether (b. p. 77–115°) and the insoluble portion was recrystallized from 95% ethanol. From the ethanolic solution was obtained 1.4 g. (14%) of a solid, the hydrochloride of triphenyl-(*m*-dimethylaminophenyl)-silane, which melted with decomposition at 210–211°. The quantity of unreacted triphenyl-(*p*-bromophenyl)-silane (mixed m. p.) recovered from the petroleum ether was 4.2 g. (42%). A viscous oil was also obtained. In a second experiment conducted in refluxing ether for thirty-eight hours, the yield of the hydrochloride was 1.5 g. (15%). The quantity of starting silane recovered was 4.1 g. (41%), and a viscous oil was obtained.

On the basis of the quantities of triphenyl-(*p*-bromophenyl)-silane entering into the reaction, the yields of the hydrochloride of triphenyl-(*m*-dimethylaminophenyl)-silane were 24.5 and 25.8%, respectively.

In each of two other experiments using the same quantities of starting materials as mentioned above, most of the ether was removed by distillation and replaced by 100 ml. of pure benzene, and the suspension refluxed for approximately forty hours. From the first run the products obtained were 3 g. (30%) of the hydrochloride, 4 g. (40% recovery) of triphenyl-(*p*-bromophenyl)-silane, and a viscous oil; and from the second run the products were 3.2 g. (32%) of hydrochloride, 4.1 g. (41% recovery) of triphenyl-(*p*-bromophenyl)-silane, and an oil. A mixed melting point determination of the hydrochlorides formed in each experiment showed no depression.

In these latter reactions, the yields of the hydrochloride of triphenyl-(*m*-dimethylaminophenyl)-silane, based on the amount of triphenyl-(*p*-bromophenyl)-silane reacting, were 50 and 55%, respectively.

Anal. Calcd. for $C_{26}H_{26}NClSi$: N, 3.4; Cl, 8.5; Si, 6.7. Found: N, 3.3; Cl, 8.6; Si, 6.6.

The oils formed in these reactions have not as yet been identified. Possibly these non-crystallizable liquids which decompose to a glass in attempts to distil them might contain some of the normal condensation product: triphenyl-(*p*-dimethylaminophenyl)-silane hydrochloride.

Triphenyl-(*m*-dimethylaminophenyl)-silane.—To 9.4 g. (0.034 mole) of triphenylchlorosilane dissolved in 50 ml. of ether was added 0.0375 mole of *m*-dimethylaminophenyllithium (prepared from 0.043 mole of *m*-bromodimethylaniline and 0.09 g. atom of lithium in 87% yield). Color Test I[9] was negative during the addition, and became positive only after an excess of the organolithium compound had been added. This indicates prompt reaction. The mixture was hydrolyzed and worked up in the customary manner. The yield of crude product, melting at 90–95°, was 11 g. (85%). The product was recrystallized from petroleum ether (b. p. 77–115°) to a constant melting point of 95–96°. The yield of pure triphenyl-(*m*-dimethylaminophenyl)-silane was 7.5 g. (58%).

Anal. Calcd. for $C_{26}H_{25}NSi$: N, 3.7; Si, 7.4. Found: N, 3.7; Si, 7.3.

Identification of the Product of Amination.—A portion of the amination product was dissolved in ethanol and gently heated with a solution of 10% sodium hydroxide dissolved in 50% ethanol. The precipitated free base was recrystallized from ethanol and melted at 94–95°. A mixture of this compound and authentic triphenyl-(*m*-dimethylaminophenyl)-silane (m. p. 95–96°) melted at 95–96°.

An ethereal solution of authentic triphenyl-(*m*-dimethylaminophenyl)-silane was treated with anhydrous hydrogen chloride, and the precipitate that formed was recrystallized from 95% ethanol. The melting point of this hydrochloride was 210–211° dec. The melting point of a mixture of this hydrochloride with that of the amination product was 210–211° dec.

Each free base formed a picrate melting with decomposition at 203–205°, and a mixed melting point showed no depression.

Anal. Calcd. for $C_{32}H_{28}O_7N_4Si$: N, 9.36; Si, 4.68. Found: N, 9.4; Si, 4.4.

The authors wish to thank Dr. S. V. Sunthankar for the *m*-bromodimethylaniline used in this study.

Summary

It has been shown that triphenyl-(*p*-bromophenyl)-silane undergoes a rearrangement reaction with lithium dimethylamide to form triphenyl-(*m*-dimethylaminophenyl)-silane.

The authentic specimen of triphenyl-(*m*-dimethylaminophenyl)-silane was prepared by interaction of triphenylchlorosilane and *m*-dimethylaminophenyllithium.

(9) Gilman and Schulze, *ibid.*, **47**, 2002 (1925).

AMES, IOWA RECEIVED JULY 21, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Naphthoquinone Antimalarials. XXIV. A New Synthesis of Lapinone

BY GEORGE FAWAZ[1] AND LOUIS F. FIESER

Preceding papers of this series have described investigations leading to the discovery of a drug, coded as M-2350, of promise as a curative antimalarial. We now propose the name lapinone, in recognition of the fact that the original clue came from observation of weak antimalarial activity of naphthoquinones resulting from Samuel C. Hooker's studies in the lapachol series. In an initial clinical trial conducted at the American University, Beirut, Lebanon, nine patients with primary vivax malaria treated with 2 g. of lapinone per day for four days (intravenous injection in gelatin solution[2]). All patients were promptly relieved of fever and parasites; two had relapses two and three weeks after treatment; one was free of symptoms for ten months and then either relapsed or was reinfected; and the other six have been without relapse for periods of thirteen to fifteen months after treatment.

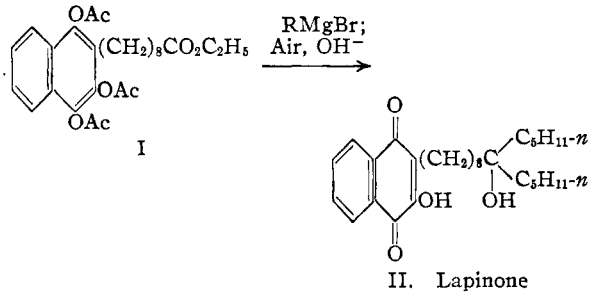
Lapinone was originally synthesized by one of us (G.F.)[3] by a Grignard reaction on the hydroquinone triacetate I and subsequent air oxidation. These reactions proceeded well, as did the preparation of I from ethyl ω-(3-hydroxy-1,4-naphthoquinonyl-2)-nonanoate, but the latter substance was available in only very low yield by peroxide alkylation of hydroxynaphthoquinone.[4] The present investigation was thus aimed

(1) On leave of absence in 1945–1946 from the Department of Biochemistry, American University, Beirut, Lebanon; present address; Department of Pharmacology, American University.

(2) Fieser, Leffler and co-workers, THIS JOURNAL, **70**, 3155 (1948), see Note Added to Proof.

(3) Fieser, Leffler and co-workers, *ibid.*, **70**, 3210 (1948).

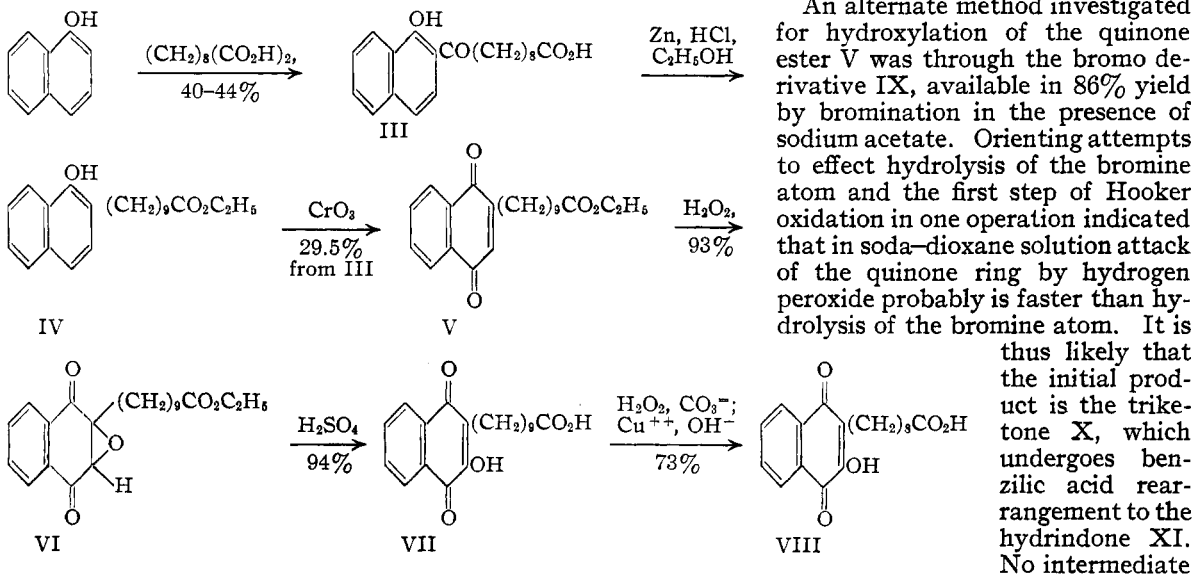
(4) Fieser and Turner, *ibid.*, **69**, 2338 (1947).



I II. Lapinone

at development of a better route to the quinone ester intermediate. The plan was to acylate 1-naphthol at the 2-position with a group capable of being transformed into $-(CH_2)_8CO_2H$ and then introduce the remaining oxygen functions.

Friedländer[5] found that α-naphthol can be acetylated efficiently at the 2-position by the action of acetic acid in the presence of zinc chloride. According to an observation by Cram[6] that we have confirmed, the condensation of monobasic acids of higher molecular weight by the same method affords only 35–40% of the 2-acyl derivatives.



We found, however, that lauroyl, myricoyl, cyclohexylbutyryl and related groups can be introduced at the 2-position in high yield by condensation of the appropriate acid with α-naphthol in the presence of boron fluoride etherate. Condensations with dibasic acids offering possibility for obtaining the desired acid side chain were unpromising. Undecylenic acid gave only a tar, and reaction with sebacamidic acid proceeded in only 45% yield. Condensation of α-naphthol with sebacic acid under catalysis by boron fluoride gave as the main product, even when sebacic acid was taken in excess, 2-sebacoyl-bis-1-naphthol (ArCO-$(CH_2)_8$COAr). It was found, however, that when zinc chloride is used as catalyst 2-sebacoyl-1-naphthol (III) is the chief product and can be separated from a small amount of the bis-product and obtained easily in 40–44% yield. The reagents are cheap and the process simple.

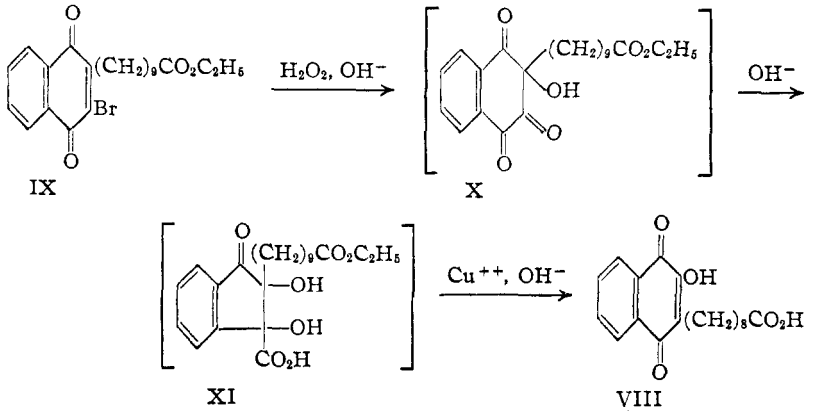
Clemmensen reduction of the keto acid III in alcoholic solution afforded the reduced ester IV, and it was found that this can be converted into the quinone ester V by oxidation with chromic acid. The yield is not high but the process is very simple. The oxide VI is obtained in high yield and can be converted by treatment with 96% sulfuric acid and subsequent acid hydrolysis into the hydroxynaphthoquinonyldecanoic acid VII. Hooker oxidation by the improved two-step process[7] was conducted satisfactorily on a large scale (172 g.) and afforded the required intermediate hydroxynaphthoquinonylnonanoic acid (VIII). For the preparation by this process of approximately 400 g. of lapinone for clinical study and pharmacological documentation we are indebted to Lin Tsai and Eva Kjelland-Mørdre, with supervision and collaboration of Drs. Huang-Minlon, J. Szmuszkovicz and Eleanor M. Behrmann.

An alternate method investigated for hydroxylation of the quinone ester V was through the bromo derivative IX, available in 86% yield by bromination in the presence of sodium acetate. Orienting attempts to effect hydrolysis of the bromine atom and the first step of Hooker oxidation in one operation indicated that in soda–dioxane solution attack of the quinone ring by hydrogen peroxide probably is faster than hydrolysis of the bromine atom. It is thus likely that the initial product is the triketone X, which undergoes benzilic acid rearrangement to the hydrindone XI. No intermediate was isolated, but treatment with copper sulfate and alkali following reaction with hydrogen peroxide and soda gave the desired nonanoic acid VIII. The yield was only 40% and nonane-1,9-dicarboxylic acid was isolated as a by-product; hence this route is less satisfactory than that through the oxide.

Experimental Part[8]

2-Acyl-1-naphthols.—Condensation of α-naphthol (1 mole) with cyclohexylbutyric acid (0.5 mole) and freshly fused and powdered zinc chloride (2 moles) for thirty minutes at 140° gave 2-cyclohexylbutyryl-1-naphthol, m. p. 103–104°, in agreement with results of Cram.[6] **2-(γ-*p*-Phenoxyphenylbutyryl)-1-naphthol,** m. p. 121–

(5) Friedländer, *Ber.*, **28**, 1950 (1895).
(6) D. J. Cram, Dissertation, Harvard University, 1947.
(7) Fieser and Fieser, THIS JOURNAL, **70**, 3215 (1948).
(8) Experiments by G. Fawaz except as noted.



IX X XI VIII

123° from alcohol, was obtained by the same procedure in 35% yield[9].

Anal. Calcd. for $C_{26}H_{22}O_3$: C, 81.65; H, 5.81. Found: C, 81.81; H, 5.97.

The yield was not improved by use of stannic acid as catalyst. Fries rearrangement of the cyclohexylbutyryl esters of α-naphthol and 4-chloro-1-naphthol with aluminum chloride was unsuccessful.

The following procedure was the best found for condensation of monobasic acids: a mixture of 1 mole of the acid or acid chloride, 1.03 moles of α-naphthol and 750 cc. of 45% boron fluoride etherate was heated on the steam-bath for four to five hours, water was added and the mixture heated on the steam-bath to remove the ether and then cooled. The gummy mass initially consisting of a boron fluoride complex was triturated with water and washed by decantation and then either crystallized from alcohol or dioxane–alcohol or boiled with alcohol to completely decompose the complex. No advantage was seen in use of the acid chloride or naphthol ester in place of the free acid. The yields given below are for purified products. Cyclohexylbutyrylnaphthol (m. p. 103–104°) and phenoxyphenylbutyrylnaphthol (m. p. 121–123°) were obtained in 80 and 90% yield, respectively.

4-Chloro-2-cyclohexylbutyryl-1-naphthol: m. p. 104–105° from ligroin or alcohol, yield 72%.

Anal. Calcd. for $C_{20}H_{25}O_2Cl$: C, 72.60; H, 7.01. Found: C, 72.81; H, 6.94.

2-Lauroyl-1-naphthol: m. p. 75–77° from alcohol, yield 82%.

Anal. Calcd. for $C_{22}H_{30}O_2$: C, 80.97; H, 9.21. Found: C, 80.97; H, 9.30.

2-Myricoyl-1-naphthol: m. p. 80–82° from alcohol, yield 83%.

Anal. Calcd. for $C_{24}H_{34}O_2$: C, 81.31; H, 9.67. Found: C, 81.46; H, 9.65.

2-ω-Bromoundecoyl-1-naphthol, m. p. 104–105° from dioxane–alcohol, yield 75%.

Anal. Calcd. for $C_{21}H_{27}O_2Br$: C, 64.46; H, 6.96. Found: C, 64.53; H, 7.06.

2-Sebacamidoyl-1-naphthol: m. p. 143–145° from alcohol, yield 45%.

Anal. Calcd. for $C_{28}H_{35}O_3N$: C, 73.38; H, 7.70. Found: C, 73.56; H, 7.90.

Condensation with undecylenic acid gave a tarry product that could not be purified. Condensation of α-naphthol (2 moles) with sebacic acid (1 mole) in the presence of boron fluoride etherate gave **2-sebacoyl-bis-1-naphthol**, m. p. 182–183° from dioxane, in 70% yield.

Anal. Calcd. for $C_{30}H_{30}O_4$: C, 79.27; H, 6.65. Found: C, 79.53; H, 6.82.

The bis-compound was the main product formed even though the acid was used in excess or replaced by the mono ester or the diester.

(9) Acid: Huang-Minlon, THIS JOURNAL, 68, 2487 (1946).

2-Sebacoyl-1-naphthol (III).—A 200-g. portion of sebacic acid was melted in a flask equipped with a thermometer and mechanical stirrer and the temperature was brought to 135–137° and maintained at this point during addition of 140 g. of freshly fused and finely powdered zinc chloride (granulated *Reagent* grade chloride can be used after being dried over phosphorus pentoxide), followed by 100 g. of α-naphthol introduced in five minutes. Heating and stirring were continued for thirty minutes longer and the melt was poured into water with vigorous stirring. The granular product was collected and washed with hot water and then with a little cold alcohol; it was then boiled with 500 cc. of alcohol, cooled, filtered, and washed with cold alcohol until the filtrate was colorless (300 cc.). The dried material was then boiled with 400 cc. of acetic acid and the solution filtered through a hot funnel from an undissolved residue consisting mainly of sebacoyl-bis-naphthol (above).

To remove further traces of the bis-product, the crude sebacoylnaphthol that crystallized from the acetic acid filtrate was treated in one of two ways. (a) It was boiled for five minutes with ten parts of ethyl acetate and the solution was filtered hot from a residue consisting of mono- and bis-product; the filtrate on cooling deposited 90–100 g. (40–44%) of crystals melting at 136–137° to a clear fluid. (b) The crude acid was boiled for at least ten minutes with 8% sodium bicarbonate (1.5 g. of bicarbonate per g. of material) and the solution filtered hot from the bis-product and neutralized cautiously while hot with hydrochloric acid. Crystallization from acetic acid then gave material of the same quality and yield as in (a). The pure acid melts at 137.5–139°.

Anal. Calcd. for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 73.41; H, 7.55.

Reduction of 2-Acyl-1-naphthols.—Wolff-Kishner reduction of the ketones by the procedure of Huang-Minlon[9] afforded nitrogen-containing products. Thus 2-aceto-1-naphthol (15.7 g.) yielded a product, m. p. 208–209° from benzene–ligroin.[10]

Anal. Calcd. for $C_{12}H_{10}N_2$: C, 79.10; H, 5.53; N, 15.38. Found: C, 79.50; H, 5.22; N, 15.39.

The acylnaphthols were recovered unchanged on attempted Clemmensen–Martin reduction but could be reduced with zinc and acid in alcoholic solution by the procedure described below. The crude reduction products from 2-cyclohexylbutyryl-1-naphthol and its 4-chloro derivative both yielded on chromic acid oxidation 2-cyclohexylbutyl-1,4-naphthoquinone, m. p. 74–75°, identical with a previous sample.[11]

Ethyl ω-(1,4-Naphthoquinonyl)-2-decanoate (V).—A solution of 100 g. of 2-sebacoyl-1-naphthol in 2 l. of 95% alcohol was treated with 500 cc. of 36% hydrochloric acid and 100 g. of freshly poured zinc amalgamated by shaking for fifteen minutes with 10 g. of mercuric chloride in 8 cc. of 36% hydrochloric acid and 140 cc. of water. The mixture was refluxed vigorously for seven hours, diluted with 2.5 volumes of water, and the oily ethyl ω-(1-hydroxy-2-naphthyl)-decanoate (IV) collected by ether extraction. After removal of last traces of ether in vacuum at a temperature not exceeding 50°, the oil (about 100 g.) was dissolved in 800 cc. of acetic acid and treated with a solution of 120 g. of chromic anhydride in 75 cc. each of water and acetic acid, added over thirty minutes. The temperature was maintained at 50° by cooling during the addition; when the temperature began to drop the flask was placed in a bath maintained at 67 ± 2° for five hours.

(10) For structure, see Huang-Minlon, *ibid.*, 71, 3301 (1949).

(11) Fieser, Leffler and co-workers, *ibid.*, 70, 3212 (1948).

The green solution was then diluted with 2.5 volumes of water and the dark sticky precipitate was collected the next day, crystallized from 250 cc. of acetic acid-water (5:1), and the yellow needles washed with 100 cc. of acetic acid-water (1:1); m. p. 73–74°. The yield varies with the quality of the starting material and size of batch. The average yield in several 100-g. runs was 32 g. (29.5% over-all from the keto acid); in 30-g. runs yields as high as 37% were obtained. The pure ester crystallizes from acetic acid or methanol in long yellow needles, m. p. 74–75°.

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.15; H, 7.92. Found: C, 74.04; H, 8.06.

ω-(1-Hydroxy-2-naphthyl)-decanoic acid was prepared from 2-sebacoyl-1-naphthol by hydrogenation over copper chromite at 100° and 3000 lb. and also by Clemmensen-Martin reduction[12] (acetic acid-water-hydrochloric acid-toluene; yield 72.3%). The acid is very soluble in acetone, benzene or alcohol and slightly soluble in ligroin. Crystallization from benzene-ligroin raised the m. p. to 96–97.5°.

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 76.39; H, 8.33. Found: C, 76.50; H, 8.23.

The methyl ester,[13] prepared from 10 g. of acid, 50 cc. of methanol and 1 cc. of boron fluoride etherate (refluxed one hour) and crystallized from ligroin, melted at 60–62°.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59: Found: C, 77.03; H, 8.45.

The ethyl ester[13] prepared similarly, melted at 52°.

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.16; H, 8.83. Found: C, 77.15; H, 8.87.

Methyl ω-(1,4-Naphthoquinonyl-2)-decanoate, prepared by oxidation of the naphthol ester, melted at 63–64°.

Anal. Calcd. for $C_{21}H_{26}O_4$: C, 73.65; H, 7.65. Found: C, 74.01; H, 7.78.

Ethyl ω-(3-Bromo-1,4-naphthoquinonyl-2)-decanoate. (IX).—A mixture of 35.6 g. of the quinone ester, 200 cc. of acetic acid, 24 g. of anhydrous sodium acetate and 6 cc. of bromine was shaken in a glass-stoppered flask for about six hours, or until all the sodium acetate had dissolved, and let stand in the dark for eight days. The bromo ester that separated was collected (filtrate saved), washed with 50% methanol, and crystallized from alcohol to give 30.5 g. of material, m. p. 87–88°. The acetic acid mother liquor when diluted with one volume of water and let stand afforded a precipitate that was crystallized from the alcoholic mother liquor of the first crop to give 7 g. of serviceable product, m. p. 85–87°; total yield 86%.

The analytical sample melted at 87.5–89°; the substance is light sensitive.

Anal. Calcd. for $C_{22}H_{27}O_4Br$: C, 60.70; H, 6.25. Found: C, 60.79; H, 6.16.

ω-(1,4-Naphthoquinonyl-2)-decanoic Acid.[14]—Hydrolysis of the corresponding ethyl ester in the oxidized form is not feasible because of sensitivity of the quinone ring to acids and bases. A sample of the acid for analysis was obtained by reducing the ester in alcohol with aqueous hydrosulfite, extracting the hydroquinone from the ether with repeated portions of alkaline hydrosulfite (kryptophenol), neutralizing the yellow extract with acetic acid, extracting with ether, and shaking the blue fluorescent solution with silver oxide. The quinone acid crystallized from methanol, water or dilute acetic acid in light yellow needles, m. p. 109–110.

Anal. Calcd. for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 72.95; H, 7.48.

Hydrolysis was also accomplished by shaking a solution of 1 g. of ester in 10 cc. of acetic acid with 0.5 g. of zinc dust until the color was largely discharged, adding 3 cc. of water and 2 cc. of 36% hydrochloric acid, heating for four hours on the steam-bath, adding 0.5 g. of chromic anhydride, and diluting with water; m. p. 102–103°, yield 0.90 g.

The oxide, prepared as described below, separated as microcrystals from either benzene-ligroin or dilute methanol; m. p. 99.5–100.5°.

Anal. Calcd. for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.92; H, 7.04.

Sulfuric acid converted the oxide to the hydroxyquinone, m. p. 105–106°, identical with that described below.

ω-(3-Chloro-1,4-naphthoquinonyl-2)-decanoic acid[14] was obtained unexpectedly on attempted acid hydrolysis of 2 g. of ethyl ω-(3-bromo-1,4-naphthoquinonyl-2)-decanoate in 30 cc. of acetic acid with 10 cc. of water and 3 cc. of 36% hydrochloric acid. The solution was heated on the steam-bath for four hours and on cooling deposited 1.58 g. (93%) of yellow needles. Recrystallization from ligroin containing a little benzene afforded small needles, m. p. 138–140° (positive Beilstein test).

Anal. Calcd. for $C_{20}H_{23}O_4Cl$: C, 66.20; H, 6.39. Found: C, 66.09, 66.22; H, 6.45, 6.50.

ω-(3-Bromo-1,4-naphthoquinonyl-2)-decanoic Acid.[15]—The inference that in the above experiment chlorine of the acid had displaced the quinone bromine atom was tested by duplicating the experiment with hydrobromic acid in place of hydrochloric acid. The solution darkened considerably during the heating, but treatment of the product with Norit gave bright yellow crystals, m. p. 131–132° (0.51 g. from 1 g. of ester). Further purification raised the m. p. to 132–133°.

Anal. Calcd. for $C_{20}H_{23}O_4Br$: C, 58.98; H, 5.69. Found: C, 58.71; H, 5.89.

Ethyl ω-(3-Hydroxy-1,4-naphthoquinonyl-2)-decanoate Oxide.[16]—To a solution of 100 g. of the quinone ester in 500 cc. of dioxane, a solution of 30 g. of sodium carbonate in 170 cc. of water and 70 cc. of hydrogen peroxide were added, and the mixture was kept at 70° for ten minutes, when the salts had dissolved, evolution of gas had ceased, and the oxide had partly separated as an oil. An equal volume of water was added and on cooling and scratching, the product was obtained as a granular white solid. Dried to constant weight at 40°, it melted at 54–56° and required no purification prior to hydrolysis; yield 98.0 g. (93%).

A sample crystallized from ligroin melted at 56–58°.

Anal. Calcd. for $C_{22}H_{28}O_5$: C, 70.99; H, 7.58. Found: C, 70.66; H, 7.31.

ω-(3-Hydroxy-1,4-naphthoquinonyl-2)-decanoic Acid. (a) From the Ester Oxide.[16]—One hundred grams of the above oxide ester was slowly stirred into 400 cc. of 96% sulfuric acid that had been chilled to 5°. The mixture was stirred at room temperature for one-half hour to effect complete solution (yellow changing to deep red) and then poured into 600 cc. of ice and 2 l. of acetic acid and heated on the steam-bath for two hours. (The treatment with cold sulfuric acid gives a mixture of acid and ester and the purpose of the after treatment is to effect complete hydrolysis; a little ester may appear as an oil at the start but later dissolves.) The dark solution on cooling deposited dull yellow needles (88.8 g.) m. p. 93–95° to a dark liquid. Crystallization from acetic acid gave light yellow needles, m. p. 104–105° (yellow melt); yield (dried to constant weight) 86.8 g. (94%).

(b) **From the Bromo Ester.**—The bromoquinone ethyl ester (3 g.) was dissolved in alcohol (100 cc.) and the solution treated at 25° with 5 g. of sodium hydroxide in 25 cc. of water. When the red color had developed maximum color density (colorimeter), the solution was diluted, extracted with ether, and then acidified. The material collected by ether extraction afforded 0.8 g. of hydroxyquinone acid, m. p. 92–93°. Crystallization from benzene-ligroin gave pure material, m. p. 106–107°.

Anal. Calcd. for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 70.02; H, 7.40.

(12) Experiment by Huang-Minlon.

(13) Experiment by Lin Tsai.

(14) Experiment by L. F. Fieser.

(15) Experiment by Eleanor M. Behrmann.

(16) Large scale runs by Lin Tsai and Eva Kjelland-Mørdre; initial procedure by L. F. Fieser.

ω-(3-Hydroxy-1,4-naphthoquinonyl-2)-nonanoic Acid from the Decanoic Acid.[16]—A solution of 172.2 g. of hydroxynaphthoquinonyldecanoic acid in 1250 cc. of purified dioxane mixed with 60 g. of sodium carbonate in 1250 cc. of water was swept with a stream of pure nitrogen, 100 cc. of Superoxol was added, and the red solution heated in a bath at 67–70° until decolorized (usually one or two hours). After cooling, 100 cc. of 36% hydrochloric acid was added, sulfur dioxide was bubbled in until an excess was noted by odor (about one hour), the excess was removed with a stream of nitrogen (two hours), and 400 g. of sodium hydroxide was added as a 25% solution, followed by copper sulfate solution (458 g. of crystals partially dissolved in 1 l. of water). The mixture was heated on the steam-bath for one-half hour, let stand at 25° for one-half hour, and filtered through Super-Cel. The deep red solution was then slowly stirred into 500 cc. of 36% hydrochloric acid containing pieces of ice. The light yellow precipitate melted at 116–118°; yield 120 g. (73%). One crystallization from acetic acid gave pure acid, m. p. 124.5–125.5°[4] (after drying to constant weight to decompose a solvate). Additional material is obtainable by collecting the mother liquor material in ether, shaking the solution with water and brine to precipitate dark material, and extracting with bicarbonate.

ω-(3-Hydroxy-1,4-naphthoquinonyl-2)-nonanoic Acid from Ethyl ω-(3-Bromo-1,4-naphthoquinonyl-2)-decanoate.—A solution of 10 g. of the bromoquinone ester in 50 cc. of dioxane was treated at 25° under nitrogen with 10 cc. of 30% hydrogen peroxide and a cooled solution of 2.95 g. of sodium carbonate in 50 cc. of water and heated in a bath at 70° for three hours. A yellow oil that separated initially and then slowly dissolved was identified as unchanged bromoquinone ester. The light yellow solution began to darken after two hours and 1 cc. more peroxide was added to discharge the color. The faintly yellow solution was cooled, treated with 5 cc. of 36% hydrochloric acid and excess sulfur dioxide and the excess removed with nitrogen. Oxidation was accomplished with copper sulfate (25 g.) and sodium hydroxide (7.5 g.) as above.

The crude product was crystallized from 15 cc. of acetic acid and the solvent-containing crystals were dried to constant weight at 80°; yield 3.49 g., m. p. 124.5–125.5°. A sticky solid from the mother liquor was dissolved in ether and extracted with small portions of bicarbonate solution as long as the extracts were only feebly colored. Subsequent bicarbonate extractions were deep red and afforded material from which 0.15 g. of pure hydroxyquinone acid was obtained; total yield 48%.

Acidification of the initial bicarbonate extracts afforded a yellowish solid that was obtained colorless by crystallization from water.[14] The substance is readily soluble in benzene, moderately soluble in ether, sparingly soluble in ligroin. Crystallization from benzene–ligroin gave colorless needles, m. p. 112–113.5°. The analysis indicated the structure of **nonane-1,9-dicarboxylic acid.**[17]

Anal. Calcd. for $C_{11}H_{20}O_4$: C, 61.08; H, 9.32. Found: C, 61.38; H, 9.27. The methyl ester solidifies slowly at 5° and melts at room temperature.

Notes on Subsequent Steps.[18]—Methyl ω-(3-hydroxy-1,4-naphthoquinonyl-2)-nonanoate[19] was prepared by refluxing 100 g. of acid with 1 l. of methanol and 25 cc. of boron fluoride etherate for one-half hour. On cooling and dilution with 1 l. of water, the ester separated as a bright yellow solid. For reductive acetylation 30 g. of ester was suspended with 40 g. of zinc dust in 240 cc. of acetic anhydride and 8 drops of triethylamine was added. The mixture was swirled until it became warm and the red color was discharged, cooled, and filtered from the zinc, which was washed with hot acetic acid. Water was added (3 volumes) and after hydrolysis the hydroquinone triacetate was extracted with ether. The solution was washed neutral to litmus, dried and evaporated, and the yellow oil taken up in 100 cc. of benzene. The solution was submitted to Grignard reaction with the reagent from 107 cc. of *n*-amyl bromide and 21 g. of magnesium. The reaction mixture was decomposed with 25% sulfuric acid and extracted with ether, and the dark oil obtained was dissolved in 1.5 l. of an 0.8% solution of sodium carbonate in 65% methanol, and the red solution was washed once with 300 cc. of benzene and extracted with ether in a continuous extractor. The ether extract was acidified with acetic acid, washed neutral to litmus, dried and evaporated in vacuum. The resulting lapinone (pooled total of 550 g.) was a light brown oil of analytical purity having the same antirespiratory activity as the material previously reported. The over-all yield from 30 g. of methyl hydroxynaphthoquinonylnononoate was 35 g. (90%).

Summary

The key intermediate to lapinone (II), required in quantity for clinical trial, is ω-(3-hydroxy-1,4-napthoquinonyl-2)-nonanoic acid (VIII), previously available in low yield by peroxide alkylation. An improved synthesis involves condensation of sebacic acid with α-naphthol at the 2-position, Clemmensen reduction in ethanol to give the naphthol keto ester IV, chromic acid oxidation to the naphthoquinone ester V, hydroxylation *via* the oxide to ω-(3-hydroxy-1,4-naphthoquinonyl-2)-decanoic acid (VII), and two-step Hooker oxidation to eliminate one methylene group from the side chain. Hydroxylation *via* the bromide is less satisfactory.

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(17) Walker and Lumsden, *J. Chem. Soc.*, **79**, 1194 (1901).

(18) Experiments by Lin Tsai and Eva Kjelland-Mødre; initial procedures by G. Fawaz.

(19) Fieser, THIS JOURNAL, **70**, 3244 (1948).